Responses to EPA's Development of an Acceptable Exposure Limit (AEL) for nPB Proposed Rule for n-Propyl Bromide (40 CFR Part 82, Federal Register of June 3, 2003, pp. 33284-33316)
Docket identification number:OAR-2002-0064

Comments Prepared by SLR International

Work on n-propylbromide (nPB) conducted by SLR International Corp (SLR) was mentioned repeatedly in the Proposed Rule. We have read the Proposed Rule in detail, and offer the following comments. Some of the comments focus specifically on statements made by SLR that we feel were wrongly interpreted by EPA. However, the majority of our comments focus on three primary areas of the Proposed Rule:

1. Relevance of EPA approach for developing an AEL
2. Application of Uncertainty Factors
3. Identification of toxicological endpoints

The first two areas are discussed together below, followed by comments on identification of endpoints. We end by providing a comparison of AELs identified in the proposed rule, but using more appropriate uncertainty factors.

Relevance of Approach and Use of Uncertainty Factors.

We begin by commenting on the statements made in the proposed rule regarding the validity and relevance of the acceptable exposure level (AEL) of 25 parts per million (ppm), and then focusing on comments made regarding the Occupational Exposure Level (OEL) developed by SLR International Corp (SLR).

The proposed rule states (p. 33289 of the Fed Reg) "EPA expected users to defer to any permissible exposure limit ultimately established by OSHA." This discussion continues with "because OSHA operates under a different statue, employs different methodology, and will presumably have additional data at some point in the future, OSHA's derivation of a PEL may result in a different number than the AEL we set using EPA's own methodology and the data available today."

There are several problems with these statements. First and foremost is the correct statement that "section 6 of the Occupational Safety and Health Act requires OSHA to make specific legal findings to support a standard." Therefore, it is our opinion that EPA has no jurisdiction to develop *any* AEL designed to be applicable to a workplace environment. The further fact that EPA methodology is different than OSHA methodology, and only OSHA can develop legally binding exposure levels, makes any value developed by EPA misleading because levels established using EPA methods are *not applicable* to workplace settings.

This issue is also central to our problems with EPA's interpretation of the work conducted by SLR. As stated by EPA (p. 33298 of the Fed Reg.), "based on EPA's RfC guidelines, an uncertainty factor of 3 is necessary to account for interspecies differences in pharmacodynamcs between rats and humans. Had SLR applied what EPA considers appropriate uncertainty factors, their recommended AEK would have been 17 ppm." SLR never intended to develop an RfC for nPB, but focused on developing an occupational level that would be applicable as a PEL. As discussed above, EPA and OSHA have different goals and methods when developing "safe"

concentrations. This point is clearly made in EPA's document on "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (EPA, 1994).

EPA (1994) states in Section 1.5 "occupational exposure limit (OEL) is a generic term…pertaining to human exposure to airborne contaminants. Due to their derivation methods, attendant assumptions, and intended application, they represent risk management values, and this distinction with the RfC as a dose-response estimate must be emphasized." They further state "OELs are generally time-weighted average concentrations of airborne substances to which a healthy worker can be exposed during defined work periods and under specific work conditions throughout a working lifetime, without material impairment of health. An important underlying assumption of most OELs is a workplace setting in which industrial hygienists are able to control the environments."

Since the purpose of SLR's document was to derive an OEL, we feel it is highly inappropriate, and in fact inadmissible, for EPA to incorporate uncertainty factors or other assumptions used to derive RfCs in their review, discussion, and interpretation of SLR's work, or to develop their own recommended OEL for nPB.

In fact, EPA (1994) continues by saying "the evaluation of toxicity data by agencies deriving OELs may differ from that of EPA with respect to weight-of-evidence classification, application of UFs, and other issues…the use of OELs is established to protect the average healthy worker (ages 18 to 65 years) against the adverse effects of inhaled pollutants to which they are exposed only a fraction of a day (i.e., during a typical 8-h work shift). Inhalation reference concentrations, however, are relevant to those of any age and health status and are aimed at protecting the most sensitive members of the population, assuming long-term continuous exposures. Therefore, the EPA does not endorse the use of OELs in deriving RfCs."

It is axiomatic that this statement also works in reverse, i.e., "RfCs are not endorsed in deriving OELs". Therefore, we do not agree with EPAs statement that SLR should have applied UFs consistent with EPA's RfC approach, and also do not agree with their use of UFs in deriving their own OEL. The text above indicates that EPA recognizes that, unlike RfCs, OELs incorporate all of the following:

- Exposure by healthy adults
- Fractional daily exposure
- Intermittent exposure (i.e., not every day).

Based on EPA's own statements reproduced above, it is clear that the use of a UF to account for sensitive members of a population (e.g., intraspecies UF of 3 recommended in the Fed. Reg.) is necessary when developing a RfC. However, since OELs are only intended to protect healthy adult workers, the use of a UF to account for the most sensitive individuals in a population is counter to the goals of an OEL. What is relevant and appropriate in developing an RfC is not relevant for OELs. Since SLR intended their value to be a provisional PEL, we strongly disagree that the discussed uncertainty factors are "appropriate". Therefore, a UF of 1 should be used for this parameter.

<u>EPA's Identification of Toxicological Endpoints</u>

EPA developed an AEL in accordance with EPA risk assessment guidance on derivation of a reference concentration and application of benchmark dose modeling. Using EPA-defined criteria for selection of endpoints, they selected the following for BMD modeling:

- Decreased sperm motility in F_0 and F_1 generation male rats (WIL Research 2001)
- Liver cell vacuolization in male and female rats (ClinTrials 1997).

As such, EPA accepted the liver changes, which were mild, possibly reversible, and dose-dependent only in the male, as toxicologically significant, relevant to humans, reproducible across multiple studies, and meeting quality criteria for dose-response. It should be noted that although SLR questioned the applicability of liver data, BMD modeling was also conducted for this endpoint.

EPA also questioned whether the data were test-related based on WIL Research comments that the results for sperm motility, while decreased compared to study controls, were within the historical range for the laboratory. Nonetheless, EPA modeled these data, although the change was "slight", based on statistical significance of the decrease in motility and consistency of the change with results seen at 500 and 750 ppm (i.e., evidence of a dose relationship; Fed. Reg. page 33296).

EPA questioned whether data from the F_1 generation were applicable to derivation of a workplace exposure limit (Page 33293), "particularly in relation to the potential mechanisms by which nPB exerts its effects on the reproductive system" because "the available data do not rule out the possibility that the effects on the F_1 generation occurred as a result of effects on parental germ cells (sperm or ova) or effects mediated by changes to the endocrine system." EPA went on to state that it is appropriate and protective, as well as consistent with EPA guidelines to use the endpoint observed at the lowest effect level to derive the AEL", in view of the "lack of mechanistic data on developmental and potential trans-generational effects of nPB."

We find it interesting that EPA and SLR identified the same sensitive endpoint across the many available toxicity studies on this chemical upon which to base development of an AEL or OEL. Also, results of benchmark dose modeling by EPA and SLR yielded essentially the same BMDL. The only difference in EPA and SLR recommended values lies in the application of uncertainty factors, as discussed above.

The benchmark dose-low (BMDL) calculated by EPA 169 ppm. If EPA used the same UFs as SLR, their recommended AEL would be 177 ppm (adjusting for Human Equivalent Concentration [HEC]), which is slightly higher than the value recommended by SLR. If EPA used the UF of 2 or 3 incorporated into the OEL by Doull and Rozman, their recommended AEL would range between 55 and 85 ppm, very consistent with their recommended range of 60 to 90 ppm. As is evident from these values, all three approaches yield similar AELs when appropriate uncertainty factors are applied. All of these values are more than twice the 25 ppm concentration recommended by EPA in their proposed rule.

Conclusions

To summarize, we agree with the approach, endpoint, and BMDL identified in the Proposed Rule. However, we strongly disagree with EPA's application of uncertainty factors consistent with those used to develop RfCs. RfC methods are neither pertinent nor applicable to OEL development, as stated in EPA's own guidance documents. In addition, EPA does not have the regulatory authority to develop workplace concentrations. Therefore, we strongly urge EPA to eliminate the AEL portion of the proposed rule. At the least, use of uncertainty factors should be modified consistent with the goals of an OEL. Using EPA's own words, OELs are "established to protect the average healthy worker…against the adverse effects of inhaled pollutants to which

they are exposed only a fraction of a day". Unlike EPA, SLR incorporated this goal into derivation of the OEL discussed in the Proposed Rule. Therefore, we stand behind our original recommendation.

References

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